Briefly, the present invention relates to methods of selecting an anti-aggregation molecule having the chaperone-like activity of anti-aggregation, methods of preventing or reducing aggregation, or disaggregating aggregates of an aggregating protein in subjects which do not yet have a protein aggregation disease, methods for treatment of a protein aggregation disease, and pharmaceutical compositions for prevention or treatment of a protein aggregation disease. The methods involve administering an anti-aggregation molecule, such as a monoclonal antibody that is capable of binding to a bioactive native aggregating protein or an aggregated form thereof, or administering an expression vector that encodes such an anti-aggregation molecule.

In compliance with 37 C.F.R. §1.173(c), the following statements are made. Patent claims 1-4 and added claims 5-9, 16-25 and 88-125 are pending. Originally added claims 10-15 and 26-87 have been cancelled. The following is an explanation of the support in the disclosure of the patent for the changes made to the claims.

In claim 5, the statement that the subject is one that does not have a protein aggregation disease is implicit from the original disclosure, for example, at column 6, lines 1-6, that the present invention is for use "to prevent or reduce protein aggregation in vivo". See also column 1, lines

5-9, and column 5, lines 39-41. Thus, it is an implicit disclosure that, when an invention is being used for prevention, it is administered to a subject which does not yet have the disease. The deletion of "being non-inhibitory to the biological activity of said aggregating protein", in claim 5 as well as in claims 16 and 21, does not create a written description problem and is supported, for example, in the paragraphs at column 3, lines 24-32, where it is indicated that the requirement for allowing the aggregating protein to function is only applicable to enzymes. It certainly is not applicable to β-amyloid, which has no known function. The other changes to claim 5 are merely clarifying.

The amendments to claims 9, 20, 25, 92 and 98 are merely to correct reference to "luteinizing hormone releasing hormone", which is disclosed at column 5, line 66 -- the comma was misplaced.

The amendments to claim 16 are all merely clarifying or have otherwise already been discussed with respect to claim 5.

The amendments to claim 21 are supported for the same reasons as discussed above with respect to claim 5.

New claim 100 is supported by claim 24 of the parent application as originally filed, in combination with the list of self-aggregating peptides or proteins at column 5, lines

61-67, of the present specification. The dependent claims are based on the individual proteins of the same paragraph of column 5.

Claim 107 is based on claim 7 of the parent application as originally filed, in combination with the same list of self-aggregating peptides or proteins at column 5, lines 61-67. Again, all of claims 108-125 are based on the same paragraph.

As to the amendments to the specification, the amendments to column 1, line 27; column 2, line 59; column 4, lines 49 and 50; column 6, line 62; column 7, lines 13, 31, 37, 45, 54 and 63; column 8, lines 5 and 27; and column 13, lines 22, 26 and 42, are all corrections of errors made by the Patent and Trademark Office in the printing of the patent. The correct version is present and therefore supported in the parent application as filed.

As to the remaining changes, the changes at column 2, lines 65 and 66, are merely grammatical changes to correct subject and verb correspondence. The correction to column 3, line 44, is merely another grammatical correction. The correction to column 4, line 6, corrects an obvious spelling error. The correction to column 4, lines 18 and 19, merely make the description of Figure 4 correspond to Figure 4. The nature of the hatching was changed when formal drawings were

filed in the parent case, and the description of the bars was inadvertently not changed when the formal drawings were filed, at least insofar as Figure 4 is concerned. The correctness of the changes is self-evident. With respect to column 4, line 33, there is only one bar with a left-slanting diagonal line and showing an amount of 60%. Thus, this correction is merely grammatical. At column 6, line 65, the correction is of an obvious typographical error made in the original application. The correction to column 11, line 17, is an obvious correction to make the buffer in this paragraph correspond to the description of the same buffer at column 11, line 8. While the printed patent had "Hl", this was a printing error on the part of the PTO as the original application had "Hcl". This, too, was incorrect as obviously "HCl", i.e., hydrochloric acid, was intended. The corrections at column 11, lines 23, 26 and 29, are all obvious corrections of typographical errors, as are the corrections at column 12, lines 29, 51 and 58, and column 13, line 21.

In the official action of June 29, 2001, the examiner stated that in applicant's response of January 8, 2001, the paragraph bridging pages 3 and 4 is unclear as the application as filed appeared to include an offer to surrender the patent and a consent of assignee, accompanied by a

certificate under 37 C.F.R. §3.73(b), which appeared to be proper. The examiner has requested clarification.

Applicant apologizes for the confusion which has been engendered by the papers as originally filed with this case. It is the understanding of the undersigned that on November 16, 1999, the following papers were filed in the Patent and Trademark Office.

(1) Form entitled "Reissue Patent Application Transmittal" (1 page);

(2) Form entitled "Reissue Application Fee Transmittal Form" (1 page);

(3) Form entitled "Reissue Application Declaration by the Inventor" (signed by the inventor in Hebrew) (3 pages, including one unnumbered paged referred to as an attachment to page 1);

(4) Form entitled "Reissue Application Declaration by the Assignee" (3 pages, including one unnumbered page referred to as an attachment to page 1);

(5) Form entitled "Reissue Application by the Inventor, Offer to Surrender Patent" (which includes as part of the form a consent of the assignee) and including a form entitled "Certificate under 37 C.F.R. §3.73(b)";

(6) Preliminary Amendment (including new claims 5-87);

(7) Specification and claims, including a cover page with only the top line of the printed patent, each of columns 1-18 of the printed patent and the abstract with a proposed amendment therein;

(8) Copies of the figures from the printed patent.

It is apparent that, in view of the declaration signed by the inventor that was originally filed, the "Reissue Application Declaration by the Assignee" should not have also been filed as only one such declaration is necessary. In view of the fact that the application was filed within two years of the issue date of the patent and that the claims added by preliminary amendment are broadening, patentee obviously intended that the "Reissue Declaration Signed by the Inventor" be the operative declaration. The sentence bridging pages 3 and 4 of applicant's amendment of January 8, 2001, requests that the declaration of the assignee be disregarded. The confusion noted by the examiner relates to the fact that applicant failed to note that the form relating to the offer to surrender the patent included a written consent of the assignee and a certification under §3.73(b). This is why a new consent of assignee was filed on May 25, 2001. The "Consent of Assignee" filed May 25, 2001, can be disregarded as redundant in view of the originally-filed consent of assignee, which the examiner concedes to be proper.

The previous confusion is regretted. It is hoped that this detailed explanation, together with the attached substitute declaration, discussed below, will clarify matters.

Claims 5-99 have been rejected under 35 U.S.C. §251 as being improperly broadened in a reissue application made and sworn to by the assignee and not the patentee, and claims 1-99 have been rejected as being based upon a defective reissue declaration under 35 U.S.C. §251. The examiner states that the declaration signed by the inventor is of poor quality, and the pagination is incorrect and confusing. Further, the examiner points out that the inventor's signature appears to be different in this and in the parent case. The examiner has required that applicant file a single, complete and unaltered declaration document in compliance with 37 C.F.R. §§1.63 and 1.175.

Attached hereto is a paper entitled "Substitute Reissue Declaration under 37 C.F.R. §1.175 and Power of Attorney for Reissue of Letters Patent 5,688,651. This four-page document is signed by Prof. Beka Solomon, both in English (as she signed the declaration in the parent case) and in her native Hebrew (as she signed the declaration as originally filed in this case). Please substitute this reissue declaration for all declarations previously filed in this case. Please disregard all previous copies of the explanation

of error. It is submitted that this declaration fully complies with 35 U.S.C. §251 and, as the declaration is signed by the inventor, the claims are not being improperly broadened. Reconsideration and withdrawal of these rejections and acceptance of the present application as having been properly filed, as all requirements of 35 C.F.R. §1.171-175 have been fully complied with, are respectfully urged.

Claims 5, 9-11, 15, 16, 20 (which are all in part drawn to antibody), 6-8, 12-14, 17-19, 21-52 and 85 (in part drawn to antibody) have been rejected under 35 U.S.C. §251 as being an improper recapture of claimed subject matter deliberately cancelled in the application for the patent upon which the present reissue is based. The examiner states that the instant claims 5-52 and 85 correspond in subject matter to Groups II and III of the parent application, which had been restricted out and cancelled in the parent application. More specifically, the examiner states that claims 21-52 are drawn to the same subject matter as the original claims of Group II of the parent case, and claims 5-20 and 85 are drawn to the same subject matter as the original claims of Group III of the parent case. The examiner states that the failure to file a divisional application is not considered to be an error that can be corrected by filing a reissue application. This rejection is respectfully traversed.

Claim 5, as presently amended, is not drawn to the same subject matter as original claim 24 in the parent case, which was made part of Group III by the examiner during the prosecution of the application which led to the patent presently in reissue. Group III included only claim 24 of the original application. This claim reads as follows:

> 24. The method of treating a protein aggregation disease including the steps of
>
> preparing at least one human monoclonal antibody that binds to an aggregated protein which is the cause of a disease and which reverses aggregation allowing bioactivity, and
>
> administering the monoclonal antibody.

It is, thus, clear that claim 24 is directed only to a method of <u>treating</u> a disease. Claim 5, on the other hand, is directed to a method of <u>preventing</u> a disease, and it specifically states that the anti-aggregation molecule is administered to "a subject that does not have a protein aggregation disease". A claim drawn to prevention is not directed to the same invention as a claim drawn to treatment of a disease. Accordingly, newly-amended claim 5 and those claims dependent therefrom are not subject to recapture estoppel. Claim 5 is not "of the same or broader scope than those claims that were cancelled from the original application" (*Ball Corporation v. United States*, 221 USPQ 289,

295 (Fed Cir 1984)). The claim does not even overlap with claim 24 as originally submitted. Accordingly, claim 5, as presently amended, should not be included within that group of claims which the examiner has stated is subject to recapture estoppel, but should be included among the claims listed in section 7 of the Office action, which are not directed to the same invention as any of the claims that were originally filed in the application which led to the patent which is the subject of the present reissue application.

Similarly, claim 21 is not drawn to the same invention as any of claims 7-23 of the original claims (designated Group II in the original restriction requirement) as the methods of all of claims 7-18 are directed to "treating a protein aggregation disease". Claim 21 is only directed to prevention of aggregation and reducing aggregation or disaggregating preaggregated aggregates in "a subject that does not have a protein aggregation disease". Accordingly, the invention of presently amended claim 21, and those claims dependent therefrom, should be considered to be independent and distinct from the invention of original claims 7-23.

The examiner states that claim 16 is drawn to the same subject matter as the original claim 24 of Group III. However, claim 16 is drawn to a pharmaceutical composition of an anti-aggregation molecule capable of preventing and

reducing aggregation of aggregating protein and disaggregating aggregates of aggregating protein, along with a pharmaceutically acceptable carrier. No claims to such a pharmaceutical composition were present in the 24 claims as originally submitted in the parent case. The only composition claims contained an expression vector, not the anti-aggregation molecule *per se*. Compositions containing the anti-aggregation molecule *per se* are supported, for example, at column 9, lines 24-28, of the present specification. As claims to this invention were never present in the original application (due to error without deceptive intent) and are not of the same or broader scope than those claims that were cancelled from the original application, they should not be subject to recapture estoppel. Accordingly, claim 16 and those claims dependent therefrom, including new claims 120-125, are properly examinable in the present reissue application.

Furthermore, claim 24 as originally submitted in the parent case was broadly directed to the genus of human monoclonal antibodies that bind to any aggregated protein which is the cause of a disease and which antibody reverses aggregation. New claim 100 has now been added which specifies a Markush group of particular aggregating proteins. Furthermore, dependent claims 101 to 106 are directed to

specific species of aggregating proteins, including β-amyloid, carboxypeptidase A, amylin, bombesin, etc. Thus, claim 100 is not of the same or broader scope than those claims that were cancelled from the original application. No species claims were present with respect to the method of claim 24 as originally presented in the parent case. If the examiner considers these claims to be drawn to multiple independent and distinct species, then whatever species is elected should be considered to be independent and distinct from claim 24 as originally submitted in the parent case. The same is true with respect to new claims 120-125, ultimately dependent from claim 16 herein. While the language of 37 C.F.R. §1.176 which is applicable to this case (quoted and discussed below) does not permit the examiner to require division, 37 C.F.R. §1.177 (in its present form[1] and in the form prior to the November 8, 2000, revision) specifically permits the voluntary filing of such a divisional by the reissue applicant. See §§1450-1451 of Rev. 1, 7th Edition, MPEP (Feb. 2000), attached hereto, for the practice under the old rule §1.176 under which the present application is being

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[1] Note that FR 65:54645 states:

> The changes to §1.177 relating to divisional reissues are effective on the date of publication of the rule in the **Federal Register** [September 8, 2000] for all pending and new reissue applications.

examined. If the examiner chooses to make a species election requirement in this case among the species enumerated in claim 100 and/or claim 20, applicant will voluntarily restrict the claims to the elected species and retain the option of filing a divisional on other species at an appropriate time.

The same logic applies for new claim 107, which is directed to a Markush group of aggregating proteins, and dependent claims 108-113, drawn to specific ones. These claims are different from any of the claims originally submitted in the parent case. Claim 7 as originally filed in the parent case was broadly drawn to any anti-aggregation molecule that binds to any aggregating protein. It should be noted that none of the claims as originally submitted in the parent case depended from claim 7 of the parent case. Claim 9 as originally filed in the parent case, which is specifically directed to anti-β-amyloid proteins, was dependent from claim 5 of the parent case, which is in Group I, and not from claim 7 of the parent case, which is in Group II of the restriction requirement made in the original application. Accordingly, if the examiner considers the species of the Markush group of claim 107 and of individual claims 108-113 to be drawn to multiple independent and distinct species, then whatever species is elected should be considered to be independent and distinct from claim 7, as originally submitted in the parent

case. Again, if the examiner chooses to make a species election requirement in this case among the species enumerated in claim 107, applicant will voluntarily restrict the claims to the elected species and retain the option of filing a divisional on other species at an appropriate time.

Claims 10-15 and 26-87 have now been deleted in order to facilitate further prosecution of this case. None of the remaining claims are directed to claims of the same or broader scope than those claims which were cancelled from the original application and, therefore, prosecution thereof is not barred by the recapture rule. Reconsideration and withdrawal of this rejection insofar as it might apply to any of the presently amended claims are, therefore, respectfully urged.

The examiner states that newly-submitted claims 5 (in part), 11, 15, 16, 20, 53-75, 76-79 (in part), 80-84, 85 (in part) and 86-99 are directed to inventions that are independent or distinct from the invention originally claimed. The examiner's reference to "in part" is understood as meaning to the extent that they do not read on the situation where the anti-aggregation molecule is a monoclonal antibody. The examiner states that the claims to a method of selecting an anti-aggregation molecule in an *in vitro* assay have been constructively elected by original presentation for

prosecution on the merits in the parent case and, accordingly, the remaining claims have been rejected under 35 U.S.C. §251 as being directed to inventions that are not directed to the same general invention in that the claims are now directed to new inventions, citing MPEP §§1412.01 and 1412.03. Further, the examiner states that the claims are directed to inventions that broaden the scope of the inventions claimed in the original patent by claiming different inventions and, therefore, these claims are improperly broadening the inventions. This rejection is respectfully traversed.

First of all, with respect to the examiner's comment about the claims broadening the inventions, applicant agrees that the present claims broaden the inventions originally issued in the patent whose reissue is being sought by the present application. However, as the present application was filed within two years of the issue of that patent and as a properly executed declaration by the inventor is of record in this case, such broadened claims are permissible in accordance with the first paragraph of 37 C.F.R. §1.173(a).

To the extent that this rejection is effectively a restriction requirement, inviting applicant to file divisional applications, the examiner's attention is drawn to the fact that current Rule 37 C.F.R. §1.176 is <u>not applicable to the present application</u>. The current version of 37 C.F.R. §1.176

became effective on November 7, 2000, and states at §1.176(b) that restriction between subject matter of the original patent and previously unclaimed subject matter may be required and that, if such restriction is required, the subject matter of the original claims will be held to be constructively elected. However, the rule promulgation for the change that resulted in the presently-worded §1.176 explicitly states, at Federal Register 65:54644 (September 8, 2000):

> Elimination of the prohibition against restriction in divisional application under §1.176 is effective for reissue applications filed on or after the date that is 60 days after the date of publication in the **Federal Register**.

Thus, the new wording of 37 C.F.R. §1.176, which eliminates the prohibition against requiring divisional applications, is only effective for reissue applications filed on or after November 7, 2000. As the present application was filed on November 16, 1999, the version of 37 C.F.R. §1.176 which was in existence on that date is applicable to the examination of the present application. Old §1.176, which is applicable to the examination of the present application, states:

> An original claim, if re-presented in the reissue application, is subject to reexamination, and the entire application will be examined in the same manner as original applications, subject to the rules relating thereto, excepting that division will not be required.

Thus, under the rule applicable to this case, restriction requirements are improper. See MPEP §1450 of the 7th Edition, Rev. 1, Feb. 2000, attached hereto, for a description of the practice under old rule §1.176, which is applicable in this case. As the examiner has apparently taken the position that the claims subject to the rejection in section 7 of the official action are not subject to the recapture estoppel rejection of section 6 of the official action, all of these claims must now be examined on the merits by the examiner. Accordingly, reconsideration and withdrawal of this rejection (restriction requirement) and examination on the merits of all of the claims now present in the case are respectfully urged.

The examiner has noted that text is missing from pages 2, 3, 5, 10, 13, 14, 16, 17 and 18 at the top due to improper margin size. The examiner has requested that the missing text be submitted in the form of substitute pages or a substitute specification in its entirety with proper margins.

Attached hereto is a substitute specification, complying with present Rule 37 C.F.R. §1.173(a)(1) in double-column format with the proper margins, including the amended abstract. Please substitute this specification for that originally submitted with the case. Applicant certifies that, except for the differences in the margins and the format layout, the specification submitted herewith is identical to

the specification as originally filed in the case and, therefore, no new matter is present.

It is noted that the examiner has indicated that claims 1-4 would be considered allowable if the new substitute Declaration is submitted. As the new substitute Declaration has been submitted, official acknowledgement of the allowability of claims 1-4 is respectfully urged.

It is submitted that all of the claims now present in the case fully comply with 35 U.S.C. §251. As restriction requirements are impermissible in reissue applications filed prior to November 7, 2000, such as the present one, and as none of the present claims are subject to recapture estoppel for the reasons discussed above, prompt consideration on the merits and allowance of all the claims now present in the case are earnestly solicited.

Respectfully submitted,

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